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Complete Recovery of Immune Checkpoint Inhibitor–induced Colitis by Diverting Loop Ileostomy

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Summary: Checkpoint inhibitor–induced side effects such as diarrhea and colitis occur in up to 30% of patients. We present a case of recurrent episodes of checkpoint inhibitor–induced colitis and subsequent Fournier gangrene that resolved after ileostomy formation. Once the Fournier gangrene and colitis had resolved, the ileostomy was reversed. However, within only 4 days, another serious flare-up of colitis occurred, necessitating emergent re-formation of the ileostomy. Expertise in the management of side effects of immune checkpoint inhibitor therapy is currently limited. Although most side effects are mild to moderate and transient, a minority of patients suffer from life-threatening complications, such as colitis. The creation of an ileostomy might be a valid treatment option in severe or recurrent colitis due to immune checkpoint inhibitor therapy. Intestinal diversion surgery may be useful if conservative treatment has failed, similar to other forms of immune-mediated intestinal inflammation.

Key Words: immune checkpoint inhibitor, colitis, ileostomy

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Immune checkpoint inhibitors (ICIs), such as programmed cell death protein-1 and programmed death-ligand 1, are monoclonal antibodies that block coinhibitory receptors on T cells to activate their cytotoxic immune function. The number of indications for ICI treatment is rising across various tumor types, with sophisticated treatment regimens being developed. Unfortunately, optimum treatment of the side effects has not been fully clarified or standardized so far.

The rate of ICI-induced autoimmune-type side effects is described in up to 96% of patients, and in 17%–59%, these are serious or life-threatening.[1]

Diarrhea is a very frequent side effect and occurs in up to 30% of patients, but is mostly of a less severe grade.[2,3] Diarrhea of grade 3–4 occurs in <10%, and clinically significant colitis is even less common, with an incidence of 5%.[4,5]

The incidence is higher in patients receiving cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)-blocking antibodies, such as ipilimumab, compared with patients receiving programmed cell death protein-1 receptor inhibitors, for example, pembrolizumab or nivolumab, which cause grade 3–4 diarrhea in only 1%–2%.[2,6,7]

Ipilimumab is a human immunoglobulin G1 monoclonal antibody that binds to CTLA-4, and enterocolitis is among the most frequent immune-related adverse event associated with its use. Diarrhea occurs in about one third of patients treated with ipilimumab, whereas colitis is observed in up to 22% of patients.[8]

The clinical picture of ICI-induced colitis is similar to severe acute colitis occurring in inflammatory bowel disease (IBD) and is defined as diarrhea combined with either abdominal pain, rectal bleeding, or mucus in stools.[1,3] It—that is, IBD may evolve into a life-threatening condition, leading to an acute abdomen, sepsis, and the requirement for surgical intervention.[3,6]

Current recommendations advocate interrupting treatment with checkpoint inhibitors when either grade I diarrhea is persistent or grade II diarrhea occurs.[3] Non-steroidal anti-inflammatory drugs should be avoided in patients treated with anti-CTLA-4 agents, as they may also lead to enterocolitis.[8]

However, the pharmacologic effects of ICI therapy last for a long time, implying that side effects may occur long after interruption or termination of treatment.[9] Most cases of diarrhea do not appear earlier than five weeks after treatment initiation, even though ICI therapy maybe already fully active, and can occur even weeks after termination of therapy.[3,9]

Treatment of colitis as a side effect of ICI therapy is similar to the treatment of colitis in IBD. Initial therapy—after exclusion of *Clostridium difficile* toxin and cytomegalovirus infection—comprises high-dose corticosteroids for 4–6 weeks. If the patient fails to respond to corticosteroids, therapy is escalated to tumor necrosis factor-alpha receptor antagonists (such as infliximab) or, more recently, anti-integrin therapy (vedolizumab); the latter may also be effective in some patients with infliximab-refractory ICI-associated colitis.[1,3,10] Recent data suggest that selective immunosuppressive therapy should be initiated even earlier in the treatment schedule of ICI-associated colitis.[10] However, one of the largest published cohorts concluded that corticosteroid and infliximab therapy rarely leads to complete resolution of colitis, with a success rate as low as 30%.[11]

CASE DESCRIPTION

Here, we present the case of a patient who developed ICI (nivolumab)-associated colitis, which was cured by ileostomy placement. After reversal of the ileostomy, the development of a further episode of severe colitis made the formation of another defunctioning ileostomy necessary, which led to rapid improvement and subsequent resolution of the colitis.

A 54-year-old male patient had been diagnosed with metastatic melanoma (initial stage IIIB) in 2016, and immunotherapy with nivolumab (300 mg) was established in November 2017. As side effects, he developed hypothyroidism, which was medically treated and, in the later course, severe xerostomia and stomatitis. Because of disease progression, 350 mg ipilimumab was added 8 months later as combined therapy with nivolumab (reduced to 120 mg). Radiotherapy with 6×5 Gy was performed due to brain metastasis, for which the patient was also taking dexamethasone 4 mg twice a day. The first episode of colitis was treated with infliximab and budesonide rectal foam (Fig. 1). In a subsequent relapse, methylprednisolone 250 mg over 3 days was added to the

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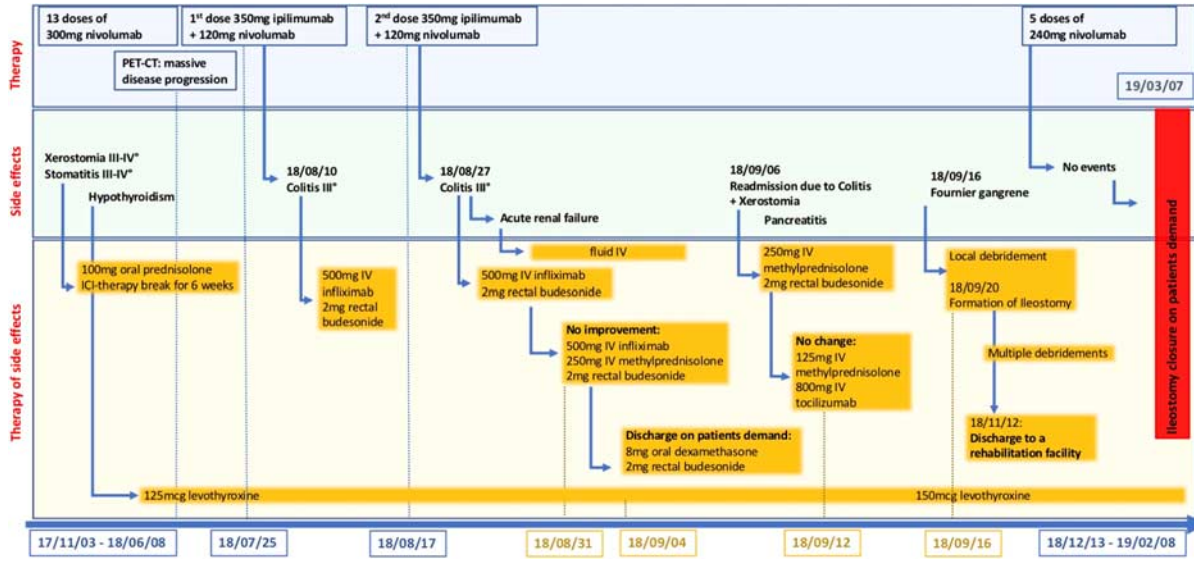

FIGURE 1. Therapeutic and clinical course of the patient. CT indicates computed tomography; ICI, immune checkpoint inhibitor; PET, positron emission tomography.

infliximab. He improved and could be discharged under 8 mg oral dexamethasone and 2 mg budesonide rectal foam.

In September 2018, a few days after discharge, he presented with another episode of colitis. In addition to this, he showed acute pancreatitis and again xerostomia as further side effects.

The colitis was treated with 250 mg IV methylprednisolone and 800 mg IV tocilizumab (Fig. 1). With this therapy, the diarrheal episodes initially improved in frequency, but, after 5 days, he developed septic shock and multiorgan failure with a Fournier gangrene, which he developed on the base of an anal fistula.

After the first surgical debridement and antibiotic treatment of the Fournier gangrene, a diverting loop ileostomy was fashioned to allow the local wound infection to heal.

The patient required treatment in the intensive care unit and underwent 6 further debridements. After 1 month, the patient was transferred to a rehabilitation facility. Colitis was not clinically apparent at this stage. Because of wound necrosis, another 1-month admission over 1-month operations was necessary.

Once complete recovery had occurred, 3 months after the episode of Fournier gangrene, treatment with a checkpoint inhibitor (nivolumab as a monotherapy) was re-established during which no clinical features of colitis were apparent.

After 5 cycles of ICI treatment, the patient requested a reversal of the ileostomy. During the preoperative workup for the ileostomy reversal, a colonoscopy was performed, which showed no signs of colitis (Fig. 2).

Few data exist with regard to postoperative complications in patients receiving ICI therapy undergoing intestinal surgery.[12] In view of the lack of data, the indication for ileostomy closure was discussed at and approved by a multidisciplinary tumor board. The patient was informed about the proposed benefits of surgery but based on little published evidence.

Closure of the ileostomy and the very early postoperative course were uneventful. Three days after the stoma reversal, the patient developed substantially increased inflammatory parameters and severe abdominal pain in all quadrants. A computed tomography scan showed free air and fluid, which was interpreted as suspicious for anastomotic leakage. An emergent explorative laparotomy was performed. To our surprise, no failure of the ileal anastomosis was found, but macroscopic evidence of severe colitis was noted. For confirmation, an intraoperative colonoscopy was performed, which confirmed severe colitis in all accessible segments of the colon (Figs. 3, 4). We, therefore, decided to refashion the loop ileostomy. The patient clinically began to stabilize on the first postoperative day, and coagulation parameters, which had previously been abnormal due to the sepsis, normalized. C-reactive protein values increased for another 2 days but then rapidly fell.

After the exclusion of *C. difficile* and cytomegalovirus colitis, anti-inflammatory medication with 125 mg IV methylprednisolone for 6 days was administered. The patient made a full recovery and was discharged in a good condition after 13 days. He was weaned off the steroids over the succeeding 6 weeks.

DISCUSSION

ICI therapies are increasingly frequently used in the treatment of different tumor types. Despite their impressive efficacy profile, they can generate immune-related adverse events, which appear to be life-threatening in up to 10% of patients.[13] To limit the severity and duration of side effects, early identification and treatment are crucial. Related to the immunologic mode of action, colitis induced by checkpoint inhibitors presents clinically similarly to colonic Crohn disease and ulcerative colitis.[8]

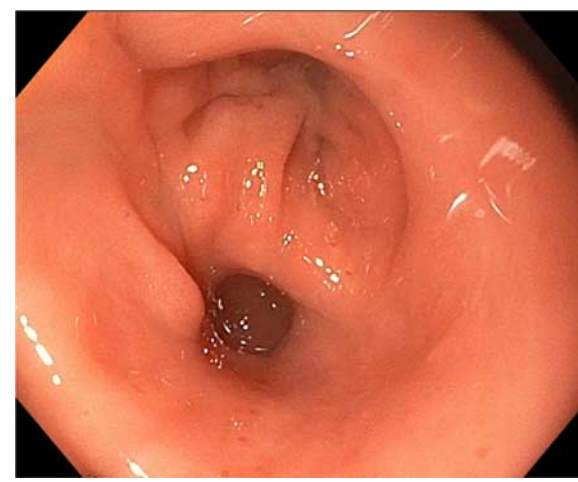

FIGURE 2. Preoperative colonoscopy without any signs of colitis.

FIGURE 3. Intraoperative colonoscopy after stoma reversal showed severe colitis, especially in the descending colon.

As well as the clinical presentation, medical treatment regimens are also comparable to those used in chronic IBD, suggesting that the underlying pathophysiology is similar. ICI-associated colitis may necessitate high doses of steroids followed by immunomodulators or biologics if the former has insufficient efficacy. As shown in a recent cohort from Australia, a sizable number of patients with acute severe colitis do not achieve resolution with medical treatment and require surgical intervention, such as a total colectomy and formation of an end ileostomy.[11]

It is well known that stool diversion surgery is effective in helping to improve an acute episode of inflammatory colitis, and one study showed that, instead of an emergent colectomy in IBD patients, the formation of a defunctioning loop ileostomy could be performed as an alternative.[14] In contrast, other authors suggest performing a subtotal rather than segmental colectomy, as anti-CTLA-4-induced colitis affects the entire colon.[8] However, two out of three patients with partial colectomy in the latter study had a colostomy formed after segmental resection and therefore no stool diversion was required. Furthermore, all of these patients had to be operated because of perforation or toxic megacolon.[8]

FIGURE 4. Intraoperative colonoscopy after stoma reversal showed severe colitis, especially in the descending colon.

We retrospectively assume that the formation of the ileostomy during the episode of Fournier gangrene helped settle the colitis that flared up again after the ileostomy was reversed. That the colitis improved a second time after repeating the surgery reinforces this hypothesis.

As previously shown, ICI-induced colitis is treated primarily with corticosteroids. However, there is emerging evidence that severe opportunistic infections can occur when steroids are administered for the treatment of ICI-induced side effects.[13,15] Although causality is unproven in this case, our patient was receiving corticosteroids when he developed Fournier gangrene and that this is an opportunistic condition that seems highly likely. The administration of corticosteroids was stopped after the diagnosis of Fournier gangrene was made.

Immune checkpoints are known to be immune exhaustion markers due to their effect in downmodulating T-cell activation and proliferation.[13,16] In chronic infections, immune checkpoints are regularly upregulated to avoid an excessive immune response.[13,16] Treatment against inhibitory immune checkpoints consequently results in an increase in immune system activity.[2] Despite their very different approaches, steroids lead to immunosuppression and ultimately produce a similar effect to immune checkpoint activation in such a setting.[13,17]

Until now, there is no evidence that the implementation of immunosuppression has a detrimental effect on the efficacy of checkpoint inhibitor therapy, even though it would theoretically appear likely.[13,17]

To the best of our knowledge, the creation of an ileostomy to allow the resolution of ICI-induced colitis has not been described in the literature so far. There are only a few case reports about ileostomy formation after colonic perforation and septic shock in ICI-associated colitis, as each case had a poor outcome.[18,19] However, colonic perforation in an immunosuppressed patient has known high mortality, and the outcome cannot be compared with prophylactic ileostomy formation, a procedure that is intended to prevent the disease in its early stage developing further.

The fundamental difference between ICI-induced colitis and IBD is that the former represents a side effect of essential medical treatment. This means that there are 2 conflicting perspectives: it would be advisable to discontinue therapy with ICIs in severe colitis to minimize infective complications, but, from an oncological point of view, it would be preferable to continue ICI therapy. More data and further research are needed to test the hypothesis that ileostomy formation in acute severe colitis could avoid further complications from immunosuppressive medication or even discontinuation of the ICI therapy, especially when severe inflammation more proximally in the gastrointestinal tract is not present.[20,21] However, on the basis of our experience in this case, we believe that the creation of an ileostomy for stool diversion could represent a valuable option for the treatment of severe ICI-induced colitis in the future.

CONCLUSION

Expertise in the management of side effects of ICI therapy is currently limited. Interruption or cessation of checkpoint inhibitor therapy due to side effects, such as severe colitis, should be discussed case by case. However, the pharmacologic effects of ICI therapy may last for a long time, meaning that side effects may not only occur a long period after interruption or termination of the treatment but also that cessation of therapy will become effective only

after a significant period of time. Although most side effects of checkpoint inhibitory therapy are mild to moderate and transient, some patients may suffer from life-threatening complications, such as colitis.

Creation of an ileostomy might, therefore, be a valid treatment option in severe or recurrent colitis due to ICI therapy.

CONFLICTS OF INTEREST/FINANCIAL DISCLOSURES

None reported. All authors have declared there are no financial conflicts of interest with regard to this work.

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